American Chemistry Council

February 27, 2015

Dr. Vincent Cogliano, Ph.D.
Director, IRIS Division
National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, N.W.
Washington, D.C. 20460

Dear Dr. Cogliano:

On behalf of the ACC Formaldehyde Panel, I want to thank you again for taking time to share your perspectives on the status of the EPA's IRIS assessment for formaldehyde. We would also like to congratulate you on your recent appointment to Program Director for the IRIS program. We look forward to providing support to EPA as the Agency works to integrate the recommendations made by the NRC Committee in its 2011 report into the revised IRIS formaldehyde assessment.

We are writing to reiterate three key points discussed during the meeting:

I. EPA Should Sponsor or Attend an Epidemiology Roundtable

First, as we've discussed with you and Dr. Olden previously, there would be great benefit from a meeting of experts for a roundtable discussion on methods for evaluating and integrating epidemiological evidence, using formaldehyde as a case study. As the NRC Committee noted in its 2011 review of the IRIS assessment, the epidemiological evidence on formaldehyde is "inconsistent." The NCI industrial workers cohort study, for example, reports an association between "peak" exposure and myeloid leukemia, but not with cumulative exposure, duration of exposure, or even number of "peaks." The analysis by the study authors also does not differentiate between different types of leukemia with potentially different etiologies – especially acute myeloid leukemia (AML) vs. chronic myeloid leukemia (CML), as has been recommended by the NRC (2011). Indeed, a reanalysis of the data from this key study will soon be published that bears on these issues.

In contrast to the results reported in the NCI cohort study, other updated cohort studies provide no clear evidence of a relationship between formaldehyde and myeloid leukemia, including the latest follow-up of the British chemical workers cohort that, "provide[s] no support for an increased hazard of myeloid leukemia, nasopharyngeal carcinoma, or other

upper airway tumors from formaldehyde exposure."[1] What, then, constitutes adequate epidemiological evidence of carcinogenicity, and what methods should be used to combine inconsistent and ambiguous results?

We strongly urge that the key epidemiology studies be carefully and objectively re-examined by a diverse group of experts using consistent and transparent methods. The roundtable approach that we have been discussing would aid this level of review, and we stand ready to help in any way to facilitate such a meeting.

II. Zhang's Work Should Be Reproduced

Second, after four years of working through FOIA requests and direct appeals, the Panel has obtained a commitment from the National Cancer Institute to enter into a Data Transfer Agreement to obtain the underlying exposure data from the Zhang et al. (2010) study. With these data, a more complete analysis of the Zhang study will be possible, including consideration of individual exposures and other characteristics that might influence the results that have been reported to be due to formaldehyde exposure. The unavailability of these data has contributed to some of the questions and uncertainties surrounding the results of the study, with these same uncertainties evident again in a more recent publication.[2] Determining whether the reported results are valid and the methodological approaches appropriate seems like necessary first steps before attempting to replicate the study on a different population.

There is a remarkable movement within the scientific community to enhance the reproducibility and transparency of studies.[3] In a Commentary published in *Nature* in early 2014, the Director of the National Institutes of Health (NIH), Francis S. Collins, M.D., Ph.D., called for enhanced reproducibility and transparency for biomedical research funded through NIH.[4] Now, following this article, top scientific journals like *Science*, *Nature* and *Toxicological Sciences* are developing guidelines for research they publish to address growing concerns over a lack of transparency and reproducibility for all studies, including those related to chemical safety.[5]

Zhang et al. (2010) was described in the 2010 draft IRIS assessment of formaldehyde as providing the "best evidence of bone marrow toxicity" to support the alleged link between formaldehyde and leukemia. However, there are well-documented criticisms of the study's

---

[1] Coggon D, Ntani G, Harris EC, and Palmer KT. Upper Airway Cancer, Myeloid Leukemia, and Other Cancers in a Cohort of British Chemical Workers Exposed to Formaldehyde. Am J Epidemiol. 2014;179(11):1301–1311

[2] Q. Lan, et al. (2014) Chromosome-Wide Aneuploidy Study (CWAS) of Cultured Circulating Myeloid Progenitor Cells from Workers Occupationally Exposed to Formaldehyde, Carcinogenesis (2015) 36 (1): 160-167.

[3] See http://www.washingtonpost.com/national/health-science/the-new-scientific-revolution-reproducibility-at-last/2015/01/27/ed5f2076-9546-11e4-927a-4fa2638cd1b0_story.html.

[4] See http://www.nature.com/news/policy-nih-plans-to-enhance-reproducibility-1.14586.

[5] See e.g., http://www.nature.com/news/journals-unite-for-reproducibility-1.16259; http://www.sciencemag.org/content/346/6210/679.full

findings.[6] In part because of these criticisms, during EPA's April 2014 formaldehyde science workshop, several scientists, including former EPA Assistant Administrator for Research & Development Dr. Bernard Goldstein, urged that the findings in the Zhang study be reproduced. Given significant questions associated with the Zhang study, we believe that the Zhang study should be re-analyzed and then, if warranted, a new study should be undertaken that attempts to reproduce Zhang using the best scientific methods available.

These unaddressed criticisms of the study providing what has been characterized by EPA as the "best evidence", combined with the ambiguous epidemiological evidence, raise serious questions as to whether EPA should proceed with its analysis of the leukemia endpoint in the revised draft IRIS formaldehyde assessment. It is imperative that these more basic scientific concerns be resolved, especially given the lack of evidence of any health effects from exposures at levels encountered in workplaces and in consumer products today.

III. EPA Should Hold a Dose Response Workshop

Third, we are concerned that Dr. Olden's commitment in his opening remarks at the leukemia workshop on April 10, 2014 for a follow-up workshop is no longer being honored. As Dr. Olden indicated, the formaldehyde data set is very extensive and complex and cannot be adequately addressed in a single two-day workshop. We understood that the next workshop would likely include discussions on dose-response. We believe a scientific workshop would assist EPA in responding to the NRC Committee criticisms of the previous 2010 draft IRIS assessment. It would also enhance EPA's efforts in evaluating and incorporating into any quantitative risk assessment the new mechanistic data regarding formaldehyde and leukemia, as well as the direction from the NRC Committee to apply alternative dose-response modeling by using Cox regression or alternative nonlinear function forms to the epidemiological data. We believe a dose-response workshop should address the following general topics:

1. *The use of the BBDR model in the formaldehyde assessment.* The NRC Committee opined on this topic in its 2011 report, calling on EPA to use the BBDR models published by Conolly et al. (2003, 2004) in the revised draft assessment and to compare the results from this model to those of the approach used in the prior draft. The NRC Committee noted many of the other adjustments to the BBDR model that had been proposed by NCEA staff in the prior draft "may not be scientifically defensible" and are not a basis for rejecting the model.

2. *Dose response curves that may be used in an IRIS risk assessment.* The 2011 NRC Committee recommended that EPA consider providing "alternative calculations that factor in nonlinearity associated with the cytotoxicity-compensatory cell proliferation mode of action and assess strengths and weaknesses of each

[6] See e.g., http://informahealthcare.com/doi/abs/10.3109/10408444.2013.818618.

approach." This recommendation stems from the Committee's concern that assessing risk of cancer associated with mutagenic mode of action poses "major uncertainties." There are questions regarding "linear models for low-dose extrapolations for a chemical that is formed endogenously and is too reactive to be measured in the body apart from portal-of-entry tissues."

3. *The mechanistic results from studies reported by Dr. Swenberg and co-workers*[7] *demonstrating that exogenous formaldehyde does not reach bone marrow in multiple species.* These results have been further supported by recent studies with additional assays by other investigators.[8] Dr. Swenberg and co-workers have also conducted recent studies to increase the understanding of mechanisms and biological pathways potentially underlying formaldehyde-induced health effects.[9] This mechanistic data is critical for decisions related to the BBDR model used in the IRIS assessment and, if this model is not considered, the development of an appropriate dose-response modeling approach.

As EPA moves forward with dose-response issues, it is important to note that use of the BBDR model has been focused on dose-response assessment for nasopharyngeal cancers - not leukemia. There remains a lack of data to support a mechanism for formaldehyde-induced lymphohematopoietic malignancies. Recent animal studies conducted by the National Toxicology Program in genetically modified susceptible species,[10] in addition to recent studies conducted by Swenberg and co-workers, provide additional evidence supporting the lack of a

---

[7] See e.g., Lu, K., Collins, L. B., Ru, H., Bermudez, E., & Swenberg, J. A. (2010). Distribution of DNA adducts caused by inhaled formaldehyde is consistent with induction of nasal carcinoma but not leukemia. *Toxicological Sciences*, 116(2), 441-51.
Lu K, Moeller B, Doyle-Eisele M, McDonald J, Swenberg J. 2011. Molecular dosimetry of N2-hydroxymethyl-dG DNA adducts in rats exposed to formaldehyde. *Chem. Res. Toxicol.* 24(2), 159-61.
Moeller B, Lu K, Doyle-Eisele M, McDonald J, Gigliotti A, Swenberg J. 2011. Determination of N2-Hydroxymethyl-dG Adducts in the Nasal Epithelium and Bone marrow of Nonhuman Primates Following 13CD2-Formaldehyde Inhalation Exposure. *Chem. Res. Toxicol.* 24: 162-164.

[8] Edrissi B,Taghizadeh K, Moeller, B, Kracko D, Doyle-Eisele M, Swenberg J and Dedon P. (2013). Dosimetry of N6‐Formyllysine Adducts Following {13C2H2}‐Formaldehyde Exposures in Rats. *Chem. Res. Toxicol.* 26:1421−1423.

[9] Rager J, Moeller B, Miller S, Kracko D, Doyle-Eisele M, Swenberg J and Fry R. (2013). Formaldehyde-Associated Changes in microRNAs: Tissue and Temporal Specificity in the Rat Nose, White Blood Cells, and Bone Marrow. *Toxicological sciences* 138(1): 36–46.
Rager J, Moeller B, Doyle-Eisele M, Kracko D, Swenberg J and Fry R. (2013). Formaldehyde and Epigenetic Alterations: MicroRNA Changes in the Nasal Epithelium of Nonhuman Primates. *Environ Health Perspect* 21:339–344.

[10] Morgan D, Dixon D, Jokinen M, King D, Price H, Travlos G, Herbert R, French J and Waalkes M. (2014). Evaluation of a Potential Mechanism for Formaldehyde- Induced Leukemia in C3B6.129F1-Trp53tm1Brd Mice. Abstract 1110f be presented at the 2014 Society of Toxicology meeting in Phoenix, AZ, March 2014.
Morgan D, Dixon D, Jokinen M, King D, Price H, Travlos G, Herbert R, French J and Waalkes M. (2015). Evaluation of a Potential Mechanism for Formaldehyde- Induced Leukemia in p53-Haploinsufficient Mice. Abstract 1637 to be presented at the 2015 Society of Toxicology meeting in San Diego, CA, March 2015.

mechanism by which formaldehyde may cause lymphohematopoietic malignances. These data would be critical in not only understanding the approach for dose-response analysis, but also in evaluating whether lymphohematopoietic malignancies should even be considered as an endpoint for a dose-response assessment.

Thus, there are a host of difficult scientific questions related to dose-response issues. EPA would benefit from a workshop in which a representative group of well-respected scientists offered their views of the evidence. Based on these concerns and recommendations, we strongly urge EPA to hold this important second public meeting on dose response.

We very much appreciate your willingness to maintain an open dialogue with the Panel. We will continue to keep EPA informed as to developments regarding new science supported by the Panel.

Sincerely,

Jackson Morrill
Director
ACC Formaldehyde Panel

Cc: Ken Olden, Director, National Center for Environmental Assessment